Carboplatin, Paclitaxel and Nivolumab
Neo-adjuvant NSCLC

Indication
Nivolumab in combination with platinum- based chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer for patients fitting the Bluteq criteria.

Regimen details

Nivolumab	**360mg**	**In 100mL sodium chloride 0.9%. Infused over 30 minutes**
Paclitaxel	**175mg/m^2**	**In 500mL sodium chloride 0.9% over 3 hours**
Carboplatin	**AUC 5**	**In 500mL glucose 5% over 30 to 60 minutes**

Cycle frequency
21 days

Number of cycles
3

Administration
Nivolumab is to be given prior to chemotherapy, via a non-pyrogenic line with a 0.2 micron to 1.2 micron filter.

Paclitaxel is to be given via a non-PVC giving set with a 0.22 micron filter, after nivolumab and before carboplatin.

Patients should be monitored for infusion reactions.

Pre-medication
(30 mins pre paclitaxel)
Chlorphenamine 10mg I.V bolus
Ranitidine 50mg 50mls Sodium chloride 0.9% Stat
Dexamethasone 20mg 100mls Sodium chloride 0.9% Stat

Emetogenicity
Moderate

Additional supportive medication
Antiemetics as per local policy, if required

Extravasation

Nivolumab – Neutral
Paclitaxel - Vesicant
Carboplatin - Irritant

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Thyroid function	14 days
Glucose	14 days
Calcium	14 days
Mg	14 days
Cortisol	14 days
Troponin T	14 days
CK	14 days
Pro-BNP	14 days
LH/FSH	3 months
Testosterone (Men only)	3 months
HbA1c	3 months
B12	3 months
Folate	3 months
Iron profile	3 months
Vitamin D (25-hydroxy Vitamin D level)	3 months
Zinc	3 months
Lipid profile	3 months
Hepatitis B surface Ag	If not previously checked
Hepatitis B core antibody	If not previously checked
HIV	If risk factors
Pregnancy test	Females of childbearing age
ECG	14 days

Investigations –pre subsequent cycles

Investigation	Validity period
FBC	48 hours
U+E (including creatinine)	48 hours
LFT (including AST)	48 hours
Magnesium	48 hours
Glucose	48 hours
Calcium	As clinically indicated
Thyroid function	Every 6 weeks unless otherwise clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/doctor. Consider immunotherapy driven toxicity as a potential reason for all changing laboratory results and discuss with a consultant if any concerns.

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine	≤ 1.5 x ULN or baseline. Recalculate carboplatin dose if creatinine has increased by >20%.
Creatinine clearance	≥ 30 mL/min
Bilirubin	≤ 1.5 x ULN
ALT/AST	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 5 x ULN
Thyroid function	Advise prescriber/doctor if not in range

Dose modifications

Immunotherapy Toxicity
Dose reduction of nivolumab is NOT permitted. If indicated, nivolumab should either be permanently discontinued or temporarily suspended.

Haematological Toxicity:

Toxicity should be grading according to the CTCAE v4.0 criteria. Following assessment, treatment should be withheld for any toxicity until resolved to grade 0/1. For dose modification, follow the general guidance below and discuss with treating clinician.

Dose Level	Carboplatin	Paclitaxel
Starting dose	**AUC 5**	**175mg/m2**
First dose reduction	**AUC 4**	**150mg/m2**
Second dose reduction	**AUC 3**	**100mg/m2**
3rd dose reductions NOT advised - discontinue chemotherapy agent.		

Toxicity	Grade	Carboplatin	Paclitaxel
Neutropenia	**Grade 4** < 0.5 x 109/L	Reduce one dose level and consider prophylactic G-CSF in subsequent cycles	Reduce one dose level and consider prophylactic G-CSF in subsequent cycles
Febrile Neutropenia	**Grade ≥ 3** Neutrophils < 1.0 x 109/L with a single temperature of >38.3ºC or a sustained temperature of ≥ 38ºC for more than one hour	Reduce one dose level	Reduce one dose level
Thrombocytopenia	**Grade 3** 25.0 to < 50.0 x 109/L	Reduce one dose level	Reduce one dose level
	Grade 4 < 25.0 x 109/L	Reduce one dose level	Reduce one dose level
Anaemia	**Grade 2** < 100 - 80 g/L	Reduce one dose level	Reduce one dose level
	Grade 3 < 80 g/L	Reduce one dose level	Reduce one dose level

	Grade 4 (life-threatening consequences)	Hold drug	Hold drug
Allergic reaction or IRR	**Grade ≥ 3**	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Only the drug causing the hypersensitivity reaction should be discontinued.
Neuropathy	**Grade 2**	No change	Reduce one dose level
	Grade ≥ 3	Discontinue	Discontinue
Creatinine clearance calculated using (Cockcroft and Gault)		Discontinue if creatinine clearance < 20 mL/min	No change
Arthralgia/Myalgia	**Grade 2** Moderate pain; limiting instrumental ADL	No change	No change
	Grade 3 Severe pain; limiting self care ADL	No change	Reduce one dose level

Immunotherapy related toxicities

Immunotherapy toxicities should be aggressively managed as can cause permanent and life-threatening complications. Refer to UKONs guidance for treatment of immune related toxicities. Available at: https://www.healthierlsc.co.uk/canceralliance/chemotherapy-protocols/immunotherapy-toxicity-guidelines

Adverse effects – for full details please consult product literature

Nausea
Alopecia
Anemia
Neutropenia
Fatigue
Diarrhoea
Elevated liver enzymes
Vomiting
Asthenia
Constipation
Rash
Peripheral neuropathy
Infusion reactions
Hypothyroidism
Hyperthyroidism
Skin reaction
Adrenal insufficiency
Arthralgia/Myalgia*

*Arthralgia/Myalgia: Consider taxane-induced pain. Arthralgia or myalgia affects 60% of patients treated with paclitaxel. Typically occurs 1-3 days after treatment and persists for 2-8 days. Should be managed with analgesia including escalation to opioid analgesia if severe. Dosing can be continued following the guidance below. In subsequent cycles, patients should be encouraged to take regular analgesia starting 24hrs pre-dose.

Significant drug interactions – for full details please consult product literature

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Phenytoin: requires close monitoring if using concurrently.

Carboplatin
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin
Yellow fever vaccine: contraindicated

Paclitaxel:
Clozapine: increased risk of agranulocytosis.
Paclitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes

THIS PROTOCOL HAS BEEN DIRECTED BY DR A FORD, MEDICAL ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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